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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
DANIEL J.	RADER	Philadelphia, Pennsylvania

☐ *Additional inventors are being named on the separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

METHODS FOR TREATING HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE-EFFECTS

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[Page 1 of 1]

Respectfully submitted,

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TYPED or PRINTED NAME Gwilym J.O. Attwell

Docket Number: UPN0026-001(Q3474)

TELEPHONE 215.665.6904

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

METHODS FOR TREATING HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE-EFFECTS

FIELD OF THE INVENTION

[0001] The present invention generally relates to therapy for hypercholesterolemia and hyperlipidemia.

BACKGROUND OF THE INVENTION

[0002] Triglycerides are common types of fats (lipids) that are essential for good health when present in normal amounts. They account for about 95 percent of the body's fatty tissue. Abnormally high triglyceride levels may be an indication of such conditions as cirrhosis of the liver, underactive thyroid (hypothyroidism), poorly controlled diabetes, or pancreatitis (inflammation of the pancreas). Researchers have identified triglycerides as an independent risk factor for heart disease.

[0003] Higher-than-normal triglyceride levels are often associated with known risk factors for heart disease, such as low levels of HDL ("good") cholesterol, high levels of LDL ("bad") cholesterol and obesity. Triglycerides may also contribute to thickening of artery walls – a physical change believed to be a predictor of atherosclerosis.

[0004] Therefore, high triglyceride levels are at least a warning sign that a patient's heart health may be at risk. In response, physicians may be more likely to stress the importance of losing weight, getting enough exercise, quitting smoking, controlling diabetes and other strategies that patients can use to protect their own cardiovascular health.

[0005] A large number of genetic and acquired diseases can result in hyperlipidemia. They can be classified into primary and secondary hyperlipidemic states. The most common causes of the secondary hyperlipidemias are diabetes mellitus, alcohol abuse, drugs, hypothyroidism, chronic renal failure, nephrotic syndrome, cholestasis and bulimia. Primary hyperlipidemias have also been classified into common hypercholesterolaemia, familial combined hyperlipidaemia, familial hypercholesterolaemia, remnant hyperlipidaemia, chylomicronaemia syndrome and familial hypertriglyceridaemia.

[0006] Hypercholesterolemia is a well-known risk factor for ASCVD, the major cause of mortality in the Western world. Numerous epidemiological studies have clearly demonstrated that pharmacological lowering of TC and LDL-C is associated with a significant reduction in

clinical cardiovascular events. Hypercholesterolemia is often caused by a polygenic disorder in the majority of cases and modifications in lifestyle and conventional drug treatment are usually successful in reducing cholesterol levels. However, in few cases, as in familial hypercholesterolemia (FH), the cause is a monogenic defect and the available treatment in homozygous patients can be much more challenging and far from optimal because LDL-C levels remain extremely elevated despite aggressive use of combination therapy. Therefore, for this group of high-risk patients, effective medical therapy is urgently needed.

[0007] A number of treatments are currently available for lowering serum cholesterol and triglycerides. However, each has its own drawbacks and limitations in terms of efficacy, side-effects and qualifying patient population.

[0008] Bile-acid-binding resins are a class of drugs that interrupt the recycling of bile acids from the intestine to the liver; e.g., cholestyramine (Questran Light®, Bristol-Myers Squibb), and colestipol hydrochloride (Colestid®, The Upjohn Company). When taken orally, these positively-charged resins bind to the negatively charged bile acids in the intestine. Because the resins cannot be absorbed from the intestine, they are excreted carrying the bile acids with them. The use of such resins, however, at best only lowers serum cholesterol levels by about 20%, and is associated with gastrointestinal side-effects, including constipation and certain vitamin deficiencies. Moreover, since the resins bind other drugs, other oral medications must be taken at least one hour before or four to six hours subsequent to ingestion of the resin; thus, complicating heart patient's drug regimens.

[0009] The statins are cholesterol-lowering agents that block cholesterol synthesis by inhibiting HMGCoA reductase--the key enzyme involved in the cholesterol biosynthetic pathway. The statins, e.g., lovastatin (Mevacor®, Merck & Co., Inc.), and pravastatin (Pravachol®Bristol-Myers Squibb Co.) are sometimes used in combination with bile-acid-binding resins. Statins significantly reduce serum cholesterol and LDL-serum levels, and slow progression of coronary atherosclerosis. However, serum HDL cholesterol levels are only moderately increased. The mechanism of the LDL lowering effect may involve both reduction of VLDL concentration and induction of cellular expression of LDL-receptor, leading to reduced production and/or increased catabolism of LDLs. Side effects, including liver and kidney dysfunction are associated with the use of these drugs (Physicians Desk Reference, Medical Economics Co., Inc., Montvale, N.J., 1997). The FDA has approved

atorvastatin (an HMGCoA reductase inhibitor developed by Parke-Davis) (Warner Lambert) for the market to treat rare but urgent cases of familial hypercholesterolemia.

[0010] Niacin, or nicotinic acid, is a water soluble vitamin B-complex used as a dietary supplement and antihyperlipidemic agent. Niacin diminishes production of VLDL and is effective at lowering LDL. In some cases, it is used in combination with bile-acid binding resins. Niacin can increase HDL when used at adequate doses, however, its usefulness is limited by serious side effects when used at such high doses.

[0011] Fibrates are a class of lipid-lowering drugs used to treat various forms of hyperlipidemia (i.e., elevated serum triglycerides) which may also be associated with hypercholesterolemia. Fibrates appear to reduce the VLDL fraction and modestly increase HDL--however the effects of these drugs on serum cholesterol is variable. In the United States, fibrates have been approved for use as antilipidemic drugs, but have not received approval as hypercholesterolemia agents. For example, clofibrate (Atromid-S®, Wyeth-Ayerst Laboratories) is an antilipidemic agent which acts to lower serum triglycerides by reducing the VLDL fraction. Although serum cholesterol may be reduced in certain patient subpopulations, the biochemical response to the drug is variable, and is not always possible to predict which patients will obtain favorable results. Atromid-S® has not been shown to be effective for prevention of coronary heart disease. The chemically and pharmacologically related drug, gemfibrozil (Lopid®, Parke-Davis) is a lipid regulating agent which moderately decreases serum triglycerides and VLDL cholesterol, and moderately increases HDL cholesterol--the HDL_2 and HDL_3 subfractions as well as both ApoA-I and A-II (i.e., the AI/AII-HDL fraction). However, the lipid response is heterogeneous, especially among different patient populations. Moreover, while prevention of coronary heart disease was observed in male patients between 40-55 without history or symptoms of existing coronary heart disease, it is not clear to what extent these findings can be extrapolated to other patient populations (e.g., women, older and younger males). Indeed, no efficacy was observed in patients with established coronary heart disease. Serious side-effects are associated with the use of fibrates including toxicity such as malignancy, (especially gastrointestinal cancer), gallbladder disease and an increased incidence in non-coronary mortality. These drugs are not indicated for the treatment of patients with high LDL or low HDL as their only lipid abnormality (Physician's Desk Reference, 1997, Medical Economics Co., Inc. Montvale, N.J.).

[0012] Oral estrogen replacement therapy may be considered for moderate hypercholesterolemia in post-menopausal women. However, increases in HDL may be accompanied with an increase in triglycerides. Estrogen treatment is, of course, limited to a specific patient population (postmenopausal women) and is associated with serious side effects including induction of malignant neoplasms, gall bladder disease, thromboembolic disease, hepatic adenoma, elevated blood pressure, glucose intolerance, and hypercalcemia.

[0013] Homozygous familial hypercholesterolemia (hoFH) is a serious life-threatening genetic disease caused by homozygosity or compound heterozygosity for mutations in the low density lipoprotein (LDL) receptor. Total plasma cholesterol levels are generally over 500 mg/dl and markedly premature atherosclerotic vascular disease is the major consequence. Untreated, most patients develop atherosclerosis before age 20 and generally do not survive past age 30. The primary goal of therapy consists of controlling the hypercholesterolemia to delay the development of atherosclerotic cardiovascular disease (ASCVD). However, patients diagnosed with hoFH are unresponsive to conventional drug therapy and have limited treatment options. Current therapy includes several medications which together reduce LDL by up to 20% and a mechanical therapy, LDL apheresis, which is very effective but is not widely available and not well tolerated by patients. Thus, new therapies are needed to help control cholesterol and reduce the need for apheresis.

[0014] Patients with heterozygous FH can usually be successfully treated with combination drug therapy to lower the LDL-C to acceptable levels. In contrast, hoFH is unresponsive to conventional drug therapy and thus there are limited treatment options. Specifically, treatment with statins, which reduce LDL-C by inhibiting cholesterol synthesis and upregulating the hepatic LDL receptor, have negligible effect in patients whose LDL receptors are non-existent or defective. A mean LDL-C reduction of only about 5.5% has been recently reported in patients with genotype-confirmed hoFH treated with the maximal dose of statins (atorvastatin or simvastatin 80 mg/day). The addition of ezetimibe (a cholesterol absorption inhibitor) 10 mg/day to this regimen resulted in a total reduction of LDL-C levels of 27%, which is still far from optimal. Several non-pharmacological options have also been tested. Surgical interventions, such as portacaval shunt and ileal bypass have resulted only in partial and transient LDL-C lowering. Orthotopic liver transplantation has been demonstrated to substantially reduce LDL-C levels in hoFH patients, but obvious disadvantages and risks are associated with this approach. Although hoFH could be an

excellent model for gene therapy, this modality of treatment is not foreseeable in the near future due to the limitations on the availability of safe vectors that provide long-term expression of LDL receptor gene. Thus, the current standard of care in hoFH is LDL apheresis, a physical method of filtering the plasma of LDL-C which as monotherapy can transiently reduce LDL-C by about 50%. Apheresis uses affinity columns to selectively remove apoB-containing lipoproteins. However, because of rapid re-accumulation of LDL-C in plasma, apheresis has to be repeated frequently (every 1-2 weeks) and requires 2 separate sites for IV access. Although anecdotally this procedure may delay the onset of atherosclerosis, it is laborious, expensive, and not readily available. Furthermore, although it is a procedure that is generally well tolerated, the fact that it needs frequent repetition and IV access can be challenging for many of these young patients. Therefore, there is a tremendous unmet medical need for new medical therapies for hoFH.

[0015] Abetalipoproteinemia is a rare genetic disease characterized by extremely low cholesterol and TG levels, absent apolipoprotein (apo) B-containing lipoproteins in plasma, fat malabsorption, severe vitamin E deficiency, and progressive spinocerebellar and retinal degeneration. It has been determined that mutations in the MTP were the genetic cause of abetalipoproteinemia. MTP is responsible for transferring lipids, particularly TG, onto the assembling chylomicron and VLDL particles in the intestine and the liver, respectively. Although the mechanisms by which lipoproteins are formed are not completely understood, it is currently believed that the assembly of apoB containing lipoproteins requires two steps. The first step occurs within the endoplasmic reticulum that involves the synthesis of particles that contain only a small fraction of the lipid core found in the secreted lipoprotein. A larger core of lipid is added to the nascent particle in a second step. MTP is thought to be essential for the transfer of lipid to the apoB during the first step of the process. In the absence of functional MTP, chylomicrons and VLDL are not effectively assembled or secreted in the circulation and apoB is likely targeted for degradation. VLDL serves as the metabolic precursor to LDL and the inability to secrete VLDL from the liver results in the absence of LDL in the blood. The concept that MTP may regulate apoB lipoprotein assembly is supported by observations in mice models. In heterozygous knockout mice MTP mRNA, protein and activity have been reported approximately half of normal and the apoB plasma concentration was reduced about 30%. Dramatic reduction of apoB-100 concentration in plasma was also seen in liver-specific MTP knockout mice. The finding that MTP is the

genetic cause of abetaliproteinemia and that is involved in apoB-containing particles assembly and secretion led to the concept that pharmacologic inhibition of MTP might be a successful strategy for reducing atherogenic lipoproteins levels in humans.

[0016] Because of the tremendous impact on the treatment of atherosclerosis and cardiovascular disease that can be derived from the pharmacologic inhibition of hepatic secretion of apoB containing lipoproteins, several MTP inhibitors have been developed. Both *in vitro* and *in vivo* animal studies with these compounds support the concept that inhibition of MTP results in inhibition of apoB containing lipoproteins secretion and consequent reduction of plasma cholesterol levels. Interestingly, the animal studies cited above had been conducted in Watanabe-heritable hyperlipidemic (WHHL) rabbits and LDLR-/- mice, two models for hoFH.

[0017] Bristol-Myers Squibb (BMS) developed a series of compounds, including BMS-201038, as potent inhibitors of MTP-mediated neutral lipid transfer activity. These compounds are described, for example, in U.S. Patents 5,789,197, 5,883,109, 6,066,653, and 6,492,365, each of which is incorporated herein by reference in its entirety. In particular, MTP inhibitors are described throughout U.S. Patent 6,066,653, in particular in columns 3-28. In *in vitro* studies, BMS-201038 appears to inhibit lipid transfer by directly binding to MTP. In cell culture studies, the IC_{50} for inhibition of apoB secretion by BMS-201038 was much lower than that for apoAI secretion (0.8 nM vs 6.5 μM), indicating that the compound is a highly selective inhibitor of apoB secretion. The efficacy to inhibit accumulation of triglyceride-rich particles in plasma of rats after injection of Triton is similar in both fed and fasted states, suggesting that both intestinal and hepatic lipoprotein secretions are inhibited by this compound. Six-month toxicity studies were conducted by BMS in rats and dogs and their results are detailed in IND# 50,820. Doses tested were 0, 0.02, 0.2, 2.0, and 20 mg/kg in rats and 0, 0.01, 0.1, 1.0, and 10 mg/kg in dogs. Dose-related lipid accumulation in the liver and small intestine correlated with decrease in serum TG and cholesterol levels. These changes are a consequence of the pharmacologic effects of BMS-201038. In rats, but not in dogs, doses of 0.2 mg/kg and higher were associated with subacute inflammation and single-cell necrosis of hepatocytes and histiocytosis (phospholipidosis) in the lungs. The hepatic accumulation of lipids was reversed in rats at the end of a 1-month washout period. Studies in animals indicated that BMS-201038 effectively reduced plasma cholesterol levels in a dose dependent manner. BMS-201038 was found to be effective in reducing cholesterol levels in

rabbits that lack a functional LDL receptor: The ED_{50} value for lowering cholesterol was 1.9 mg/kg and a dose of 10 mg/kg essentially normalized cholesterol levels with no alteration in plasma AST or ALT. This study, conducted in the best accepted animal model for the homozygous FH, indicated that MTP inhibition by BMS-201038 might be effective in substantially reducing cholesterol levels in patients with hoFH.

[0018] Clinical development of BMS-201038 as a drug for large scale use in the treatment of hypercholesterolemia has been discontinued, because gastrointestinal side effects, elevation of serum transaminases and hepatic fat accumulation were observed, primarily at 25mg/day or higher doses.

[0019] Thus, there is a need to develop methods for treating hyperlipidemia and/or hypercholesterolemia that are efficacious in lowering serum cholesterol and LDL, increasing HDL serum levels, preventing coronary heart disease, and/or treating diseases associated with hyperlipidemia and/or hypercholesterolemia, without the side-effects associated with known treatments.

SUMMARY OF THE INVENTION

[0020] The present invention relates to methods of treating a subject suffering from a disorder associated with hyperlipidemia. The methods comprise administering to the subject an effective amount of an MTP inhibitor to ameliorate hyperlipidemia in the subject. The administration comprises at least three step-wise, increasing dosages of the MTP inhibitor.

[0021] The present invention also relates to methods for inhibiting MTP in a subject. The method comprises administering to the subject an effective amount of an MTP inhibitor to inhibit MTP in the subject. Administration comprises at least three step-wise, increasing dosages of the MTP inhibitor.

[0022] The present invention relates to kits for treating a disorder related to hyperlipidemia in a subject. The kits comprise a) a pharmaceutical composition comprising at least three sets of dosage units. The first set of dosage units provides 0.03mg/kg/day for a first interval. The second set of dosage units provides 0.1 mg/kg/day for a second interval. The third set of dosage units provides 0.3 mg/kg/day for a third interval. The kit also comprises instructions for use.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention is based on the surprising discovery that one may treat an individual who has hyperlipidemia and/or hyperlcholesterolemia with an MTP inhibitor in a manner that results in the individual not experiencing side-effects normally associated with the inhibitor, or experiencing side-effects to a lesser degree. Accordingly, the present invention provides a method of treating a subject suffering from a disorder associated with hyperlipidemia while reducing side-effects, the method comprising the step of administering to the subject an effective amount of the inhibitor to ameliorate hyperlipidemia in the subject according to a treatment regimen that reduces and/or eliminates side-effects associated with the use of the inhibitors.

[0024] Microsomal triglyceride transfer protein (hereinafter referred as MTP) is known to catalyze the transport of triglyceride and cholesteryl ester by preference to phospholipids such as phosphatidylcholine. It was demonstrated by D. Sharp et al., Nature (1993) 365:65 that the defect causing abetalipoproteinemia is in the MTP gene. This indicates that MTP is required for the synthesis of Apo B-containing lipoproteins such as VLDL, the precursor to LDL. It therefore follows that an MTP inhibitor would inhibit the synthesis of VLDL and LDL, thereby lowering levels of VLDL, LDL, cholesterol and triglyceride in humans. MTP inhibitors have been reported in Canadian patent application No. 2,091,102 and in WO 96/26205. Inhibitors have also been reported in U.S. Pat. No. 5,760,246 as well as in WO-96/40640 and WO-98/27979.

[0025] Pharmacologic inhibition of MTP with Bristol-Myers Squibb's BMS-201038, a potent inhibitor of MTP, has been shown to reduce low density lipoprotein cholesterol (LDL-C) by up to 65% in healthy volunteers with hypercholesterolemia. Despite these impressive LDL-C reductions, steatorrhea, elevation of serum transaminases and hepatic fat accumulation were observed, primarily at 25mg/day or higher doses. Thus, Bristol-Myers Squibb decided that these side effects made it unlikely that BMS-201038 could be developed as a drug for large scale use in the treatment of hypercholesterolemia.

[0026] MTP inhibitors belong to the class of polyarylcarboxamides. MTP inhibitors, methods of use and preparation thereof are known to the art skilled and are described, *inter alia*, in Canadian Patent Application Ser. No. 2,091,102, U.S. application Ser. No. 117,362, WO 92/26205 published Aug. 29, 1996, U.S. application Ser. No. 472,067, filed Jun. 6, 1995, U.S. application Ser. No. 548,811, filed Jan. 11, 1996, U.S. provisional application Ser. No.

60/017,224, filed May 9, 1996, U.S. provisional application Ser. No. 60/017,253, filed May 10, 1996, U.S. provisional application Ser. No. 60/017,254, filed May 10, 1996, U.S. provisional application Ser. No. 60/028,216, filed Oct. 1, 1996, U.S Patent 5,595,872, U.S. Patent 5,789,197, U.S. Patent 5,883,109, and U.S. Patent 6,066,653. All of the above, including structures, are incorporated herein by reference.

[0027] In some embodiments the MTP inhibitors are piperidine, pyrrolidine or azetidine compounds. In some embodiments the inhibitor is 9-[4-[4-[[2-(2,2,2-trifluoromethyl)-benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

[0028] Other cholesterol lowering drugs or delipidating drugs which may be used in the method of the invention include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin, niacin derivatives and the like.

[0029] The HMG CoA reductase inhibitors suitable for use herein include, but are not limited to, mevastatin and related compounds as disclosed in U.S. Pat. No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Pat. No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Pat. No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Pat. Nos. 4,448,784 and 4,450,171, with pravastatin, lovastatin or simvastatin being preferred. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, cerivastatin, atorvastatin, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Pat. No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Pat. No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-di-substituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Pat. No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Pat. No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

[0030] In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

[0031] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphonosulfonates disclosed in U.S. application Ser. No. 08/266,888, filed Jul. 5, 1994 (HX59b), those disclosed by Biller et al, J. Med. Chem. 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates including the triacids thereof, triesters thereof and tripotassium and trisodium salts thereof as well as other squalene synthetase inhibitors disclosed in U.S. Pat. Nos. 4,871,721 and 4,924,024 and in Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869 to 1871.

[0032] In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem.; 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, (J. Am. Chem. Soc. 1976, 98, 1291-1293), phosphinylphosphonates reported by McClard, R. W. et al, (J.A.C.S., 1987, 109, 5544) and cyclopropanes reported by Capson, T. L., (PhD dissertation, June, 1987, Dept. Med. Chem. U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary). In some embodiments the inhibitor is pravastatin, lovastatin or simvastatin.

[0033] The present invention provides methods for treating diseases or disorders associated with hyperlipidemia and/or hypercholesterolemina while minimizing side-effects ordinarily associated with the use of such inhibitors. In some embodiments, the inhibitor is an MTP inhibitor.

[0034] As used herein, the phrase "diseases or disorders associated with hyperlipidemia and/or hypercholesterolemina" refers to diseases related to or caused by elevated lipid or cholesterol levels.

[0035] In some embodiments, the disease associated with hyperlipidemia is hypercholesterolemia. In some embodiments, the disease is homozygous/heterozygous familial hypercholesterolemia. In some embodiments the disease is hypertriglyceridemia.

[0036] In some embodiments, cholesterol levels in the subject are reduced by at least 25%. In some embodiments, triglyceride levels in the subject are reduced by at least 25%. In some embodiments, apolipoprotein B levels in said subject are reduced by at least 25%.

[0037] In some embodiments, triglyceride levels achieved are less than 500 mg/dl. In some embodiments, triglyceride levels achieved are less than 300 mg/dl. In some embodiments,

triglyceride levels achieved are less than 200 mg/dl. In some embodiments, triglyceride levels achieved are less than 150 mg/dl.

[0038] In some embodiments, the ApoB/ApoA1 ratio achieved by treatment according to the present invention is from 0.25 to 1.25. In some embodiments the ApoB/ApoA1 ratio achieved is from 0.1 to 2.0. In some embodiments the apoB level achieved is from 48-130. In some embodiments the apoB level achieved is from 20-180.

[0039] In some embodiments the inhibitor lowers plasma LDL-cholesterol to at least 50% of normal LDL blood levels, and lowers triglycerides to at least 50% of normal triglyceride blood levels.

[0040] In some embodiments total cholesterol is reduced by at least 30%. In some embodiments, non-HDL cholesterol is reduced by at least 30%. In some embodiments, apoB is reduced by at least 15%. In some embodiments, LDL-Cholesterol is reduced by at least 30%. In some embodiments one or more of Total Cholesterol, high density lipoprotein (HDL) cholesterol, fasting triglycerides (TG), very low density lipoprotein (VLDL), lipoprotein (a) (Lp(a)), and Apolipoproteins A-I, A-II, B, and E are reduced by at least 30%.

[0041] Reduction of levels of blood components, including, for example, cholesterol, triglycerides, and apolipoprotein B, can be determined by comparing pre-treatment levels to levels during or after treatment according to the present invention. Methods of measuring levels of particular components of blood are well-known to those of skill in the art. For example, total plasma cholesterol and triglyceride concentrations may be determined by a modification of the Liebermann-Burchard reaction (Abell LL, Levy BB, Brodie BB, Kendall FE. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. *J Biol Chem.* 1952;195:357–362) and by the method of Kessler and Lederer after zeolite extraction, (Kessler G, Lederer H. Fluorometric measurement of triglycerides. In: Skeggs LT,Jr, eds. *Automation in Analytical Chemistry: Technicom Symposia.* New York, NY: Madiad Inc; 1965:341–344) respectively. Plasma HDL cholesterol may be estimated by the method of Allain et al (Allain CC, Poon LS, Chan GSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem.* 1974;20:470–475) using an enzymatic kit (Biotrol). LDL cholesterol may be calculated using the Freidewald formula. (Freidewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein-cholesterol in plasma without the use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499–502). Plasma apoB, apoA1, and lipoprotein(a) levels may be measured by

immunological assays as described earlier (Guo H, Chapman MJ, Bruckert E, Farriaux JP, De Gennes JL. Lipoprotein Lp(a) in homozygous familial hypercholesterolemia: density profile, particle heterogeneity and apolipoprotein(a) phenotype. *Atherosclerosis.* 1991;31:69–83) and based on laser immunonephelometry (Immuno AG).

[0042] In some embodiments, the subject is a mammal, preferably a human. In some embodiments, the subject has proven refractory to previous treatment regimens.

[0043] In some embodiments, the inhibitor has a structure as set forth in U.S. Patent 6,066653. In some embodiments, the inhibitor is BMS-201038. As used herein, the phrase "BMS-201038" refers to a compound known as N-(2,2,2-Trifluorethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'biphenyl]-2- Yl]carbonyl]amino]-1-piperidinyl]butyl]9H-fluorene-9-carboxamide, methanesulfonate.

[0044] The inhibitor of the present invention may be used alone or optionally in combination with another cholesterol lowering drug or delipidating agent and may be administered systemically, such as orally or parenterally or transdermally, to subjects in need of treatment. The dosages and formulations for the other delipidating agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

[0045] In some embodiments, the inhibitor is administered at escalating doses. In some embodiments, the escalating doses comprise at least a first dose level and a second dose level. In some embodiments, the escalating doses comprise at least a first dose level, a second dose level, and a third dose level. In some preferred embodiments, a fourth dose level is also administered.

[0046] In some embodiments, each dose level is no more than 50% of the immediately following dose level. In some embodiments, each dose level is no more than 33% of the immediately following dose level. In some embodiments, dose levels are separated by ½ log units. In some embodiments, dose levels are separated by 1 log unit.

[0047] In some embodiments, the first dose level is from about 0.02 to about 0.059 mg/kg/day. In some embodiments, second dose level is from about 0.06 to about 0.19mg/kg/day. In some embodiments, the third dose level is from about 0.2 to about 0.59 mg/kg/day. In some embodiments, the fourth dose level is from about 0.6 to about 2.0 mg/kg/day.

[0048] In some embodiments each dose level is administered to the subject for 2 days to 26 weeks. In some embodiments, each dose level is administered to the subject for 1-5 weeks.

[0049] In some embodiments the inhibitor is administered at:

(a) 0.03mg/kg/day for a first interval;

(b) 0.1 mg/kg/day for a second interval;

(c) 0.3 mg/kg/day for a third interval; and

(d) 1.0 mg/kg/day for a fourth interval.

In some embodiments the first, second, third, and fourth intervals are from about 2 days to about 6 months in duration. In some embodiments the first, second, third, and fourth intervals are from about 7 days to about 35 days in duration. In some embodiments the first, second, third, and fourth intervals are from about 2 weeks to about 4 weeks in duration. In some embodiments the first, second, third, and fourth intervals are each about 4 weeks in duration. In some embodiments the first, second, third intervals are from about 2 days to about 40 days in duration and the fourth interval is from about 2 days to about 6 months in duration.

[0050] In some embodiments the first dose level is 6.25 mg/day, the second dose level is 12.5mg/day, and the third dose level is 50mg/day. In some embodiments each dose level is from about 1 week to about 12 weeks. In some embodiments each dose level is from about 1 week to about 26 weeks. In some embodiments the first dose level is administered for 2 weeks, the second dose level administered for 4 weeks, and the third dose level administered for 4 weeks.

[0051] In some embodiments the method further comprises administration of a fourth dose level of 62.5mg/day for 4 to about 26 weeks. In some embodiments the fourth dose level is 75 mg/day for 4 to about 26 weeks.

[0052] As used herein, the phrase "minimizing side effects" refers to an amelioration or elimination of one or more side effects of the inhibitors of the present invention. In some embodiments, side effects are partially eliminated. As used herein, the phrase partially eliminated refers to a reduction in the severity, extent, or duration of the side effect of at least 25%, 50%, 75%, 85%, 90%, or preferably 95%. In some embodiments, side effects are completely eliminated. Those skilled in the art are credited with the ability to detect and grade the severity, extent, or duration of side effects. In some embodiments, two or more side-effects are ameliorated.

[0053] In some embodiments, the side-effects are GI side-effects or hepatobiliary side-effects. In some embodiments, the side effects are at least one of steatorrhea, abdominal

cramping, distention, elevated liver function tests, minor fatty liver; hepatic fat build up, polyneuropathy, peripheral neuropathy, rhabdomyolysis, arthralgia, myalgia, chest pain, rhinitis, dizziness, arthritis, peripheral edema, gastroenteritis, liver function tests abnormal, colitis, rectal hemorrhage, esophagitis, eructation, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice, paresthesia, amnesia, libido decreased, emotional lability, incoordination, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia, anaphylaxis, angioneurotic edema, and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis).

[0054] In some embodiments, amelioration of one or more side effects occurs within 2 weeks of initiation of treatment. In some embodiments, amelioration of the one or more side effects occurs within 3 weeks of initiation of treatment.

[0055] In some embodiments the amelioration of said side effect is determined by assessing the grade, severity, extent, or duration by subject questionnaire.

[0056] The present invention also provides a method for inhibiting MTP in a subject while reducing side effects comprising administering to the subject an amount of an inhibitor effective to inhibit MTP. In some embodiments, the MTP inhibitor is administered orally.

[0057] The present invention further provides a kit for treating a disorder related to hyperlipidemia in a subject. In some embodiments the kit comprises a) a pharmaceutical composition comprising at least three sets of dosage units, wherein a first set of dosage units provides 0.03mg/kg/day for a first interval, a second set of dosage units provides 0.1 mg/kg/day for a second interval, and a third set of dosage units provides 0.3 mg/kg/day for a third interval; and b) instructions for use. In some embodiments, the kit further comprises a fourth set of dosage units, said fourth set providing 1.0 mg/kg/day for a fourth interval. In some embodiments, the kit further comprises a container for storing the sets of dosage units according to a schedule for administration.

[0058] For oral administration, the pharmaceutical compositions of the present invention may take the form of solid dose forms, for example, tablets (both swallowable and chewable forms), capsules or gelcaps, prepared by conventional means with pharmaceutically acceptable excipients and carriers such as binding agents (e.g. pregelatinised maize starch,

polyvinylpyrrolidone, hydroxypropylmethylcellulose and the like), fillers (e.g. lactose, microcrystalline cellulose, calcium phosphate and the like), lubricants (e.g. magnesium stearate, talc, silica and the like), disintegrating agents (e.g. potato starch, sodium starch glycollate and the like), wetting agents (e.g. sodium laurylsulphate) and the like. Such tablets may also be coated by methods well known in the art.

[0059] By treatment is meant at least an amelioration of the symptoms associated with the pathological condition afflicting the host as well as an amelioration of the side-effects associated with the inhibitor seen in patients treated in accordance with traditional treatment regimens making use of the inhibitors. "Amelioration" is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g. symptom, associated with the pathological condition being treated, such as elevated plasma VLDL or triglyceride levels, or with a side-effect of treatment using the inhibitor, such as GI side-effects or hepatobiliary side-effects. As such, treatment also includes situations where the pathological condition, or at least symptoms associated therewith, are completely inhibited, e.g. prevented from happening, or stopped, e.g. terminated, such that the host no longer suffers from the pathological condition, or at least the symptoms that characterize the pathological condition, e.g. plasma VLDL and/or triglyceride levels are returned to normal.

[0060] As used herein, the phrase "side-effects" refers to undesired events occurring as a result of the traditional use of the inhibitors of the invention. "Side-effects" of traditional use of the inhibitors of the invention include, without limitation, steatorrhea, abdominal cramping, distention, elevated liver function tests, minor fatty liver; hepatic fat build up, polyneuropathy, peripheral neuropathy, rhabdomyolysis, arthralgia, myalgia, chest pain, rhinitis, dizziness, arthritis, peripheral edema, gastroenteritis, liver function tests abnormal, colitis, rectal hemorrhage, esophagitis, eructation, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice, paresthesia, amnesia, libido decreased, emotional lability, incoordination, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia, anaphylaxis, angioneurotic edema, and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis).

[0061] The dose administered may be adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

[0062] Preparation and formulations of the inhibitors are disclosed infra, supra, and in disclosed in Canadian Patent Application Ser. No. 2,091,102, U.S. application Ser. No. 117,362, WO 92/26205 published Aug. 29, 1996, U.S. application Ser. No. 472,067, filed Jun. 6, 1995, U.S. application Ser. No. 548,811, filed Jan. 11, 1996, U.S. provisional application Ser. No. 60/017,224, filed May 9, 1996, U.S. provisional application Ser. No. 60/017,253, filed May 10, 1996, U.S. provisional application Ser. No. 60/017,254, filed May 10, 1996, U.S. provisional application Ser. No. 60/028,216, filed Oct. 1, 1996, U.S Patent 5,595,872, U.S. Patent 5,789,197, U.S. Patent 5,883,109, and U.S. Patent 6,066,653. All of the above, including structures, are incorporated herein by reference.

[0063] For oral administration, a satisfactory result may be obtained employing the inhibitor in a daily amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 75 mg/kg, one to four times daily.

[0064] A preferred oral dosage form, such as tablets or capsules, may contain the inhibitor in a daily amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

[0065] For parenteral administration, the MTP inhibitor may be employed in a daily amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 8 mg/kg, one to four times daily.

[0066] Additional serum cholesterol lowering drugs, when present, may be employed in dosages normally employed as indicated in the Physician's Desk Reference, for each of such agents such as in an amount within the range of from about 2 mg to about 7500 mg and preferably from about 2 mg to about 4000 mg.

[0067] The inhibitor and other cholesterol lowering drug may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

[0068] The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily.

[0069] Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted

pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

[0070] Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsfuls.

[0071] Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

[0072] According to another modification, in order to more finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

[0073] Fixed combinations of inhibitors and other cholesterol lowering drugs are more convenient and are preferred, especially in tablet or capsule form for oral administration.

[0074] In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

[0075] Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

[0076] Some of the active substances described above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

[0077] The formulations as described above will be administered for a prolonged period, that is, for as long as the acid lipase deficiency exists. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed.

[0078] As used herein, the term "susceptible" refers to patients who suffer one or more side-effects when inhibitors are administered to them using traditional dosing regimes in an attempt to ameliorate hypercholesterolemia and/or hyperlipidemia.

[0079] As used herein, the phrase "traditional treatment regimens" and the like, refers to methods of treating hypercholesterolemia and/or hyperlipidemia using standard dosing, e.g. set dosing levels, etc. For example, traditional dosing methods include, for example, the use of one dosing level throughout the course of treatment.

[0080] The following examples are meant to illustrate the invention and are not to be construed to limit the invention in any way. Those skilled in the art will recognize modifications that are within the spirit and scope of the invention.

Examples

[0081] EXAMPLE 1

[0082] Formulations suitable for oral administration are prepared as described below.

[0083] Capsules containing 1 mg MTP inhibitor BMS 201,038 and capsules containing 50 mg BMS 201,038 are produced from the following ingredients.

[0084]

	1 mg capsule Amt (mg/capsule)	50 mg capsule Amt (mg/capsule)
BMS-201038*	1.1	56.9
Lactose, Hydrous, NF	ca. 30.2	ca. 99.9
Lactose, Anhydrous, NF	47.3	0.0
Microcrystalline Cellulose, NF	10.0	50.0

Pregelatinized Starch, NF	5.0	25.0
Sodium Starch Glycolate, NF	5.0	12.5
Colloidal Silicon Dioxide, NF	1.0	5.0
Magnesium Stearate, NF	0.3	0.6
Purified Water, USP or	q.s.	q.s.
Water for Injection, USP	q.s.	q.s.
Gray, Opaque, Size #0	One Capsule	One Capsule
Total Fill Weight	100.0	250.0

(*) In the 1 mg capsule this amount is expressed in terms of the amount of methane sulfonic acid salt per capsule at 100% potency. In the 50 mg capsule, this amount is expressed in terms of the free base This is equivalent to 1 mg and 50 mg (1mg capsule and 50mg capsule, respectively) of the free base.

[0085] The MTP inhibitor BMS 201,038, and colloidal silicon dioxide are blended in a suitable blender with lactose hydrous, microcrystalline cellulose, pregelatinized starch and a portion of sodium starch glycolate. The resulting blend is wet granulated with water. The wet granulation is dried in a suitable dryer. The remaining portion of sodium starch glycolate is added to the granulation and mixed therein. Magnesium stearate is added to the granulation and mixed therein. The resulting blend is filled into capsules.

[0086] EXAMPLE 2

[0087] Pravastatin tablets (10, 20 or 40 mg as described in the 1996 PDR) and MTP inhibitor (BMS 201,238) tablets may be administered as a combination in accordance with the teachings of the present invention. In addition, the pravastatin and MTP inhibitor tablets may be ground up into powders and used together in a single capsule.

[0088] EXAMPLE 3

[0089] Tablets containing 500 mg clofibrate by itself or in combination with 10 mg BMS 201,038 may be employed in separate dosage forms or combined in a single capsule form.

[0090] EXAMPLE 4

[0091] To evaluate pharmacodynamic readouts of treatment according to the present invention, the effects of treatment with BMS-201038 at 4 dose levels (0.03, 0.1, 0.3, and 1.0 mg/kg body weight) on nutritional status, hepatic fat content and pulmonary function can be determined by:

(a) Hepatic fat content as measured by MRI \ nuclear magnetic resonance spectroscopy (NMRS);

(b) Pulmonary function as measured by spirometry with DLCO;

(c) Nutritional status as measured by serum levels of fat soluble vitamins A, D, and E;

(d) international normalized ratio (INR) to evaluate vitamin K status; and plasma phospholipid inoleic acid, arachidonic acid, alpha linolenic acid and eicosapentaenoic acid by gas liquid chromatography to assess essential fatty acid intake.

[0092] EXAMPLE 5

[0093] Twenty (20) subjects are randomized in a 3:1 ratio to BMS-201038 (n=15) or placebo (n=5) in a double-blind fashion for 11-15 weeks depending on weight as described below. At the end of 11or 15 weeks, BMS-assigned subjects will continue taking the maximum tolerated dose for the remaining study (through week 39). For BMS-201038-treated patients, study drug will be initiated at 6.25 mg/d for 1 week and then will be titrated up to 12.5 mg/day for 2 weeks followed by 25 mg/day for 4 weeks and then to 50 mg/day for 4 weeks. BMS-201038 treated subjects whose weight is between 62.5 and 74.9 kg will titrate up to 62.5 mg/day for an additional 4 weeks. BMS-201038-treated subjects whose weight is $\geq$75 kg, will titrate up from 50 mg to 75 mg/day for an additional 4 weeks. Subjects who weight is < 62.5 kg will remain at 50 mg/d (or the maximum tolerated dose) for the remaining 28 weeks. Subjects who titrate up to 62.5 mg/d or 75 mg/day will remain at this dose (or the maximum tolerated dose) for the remaining 24 weeks.

[0094] Subjects randomized to placebo will take matching placebo for 15 weeks. After this time period, placebo-treated subjects will start taking BMS-201038 following the same schedule as outlined above for the original BMS-201038-treated subjects. After the dose titration schedule is complete at week 26 or 30 depending on weight, subjects will take the

maximum tolerated dose for the remaining study (through week 39) so that the entire study for all subjects will be 39 weeks in duration.

[0095] EXAMPLE 6

[0096] The tolerability and thus the effectiveness of BMS-201038 appears to be dependent on the dosing regimen. In a phase II study using BMS-201038 in patients with primary hypercholesterolemia, a dosage of 25 mg per day for 4 weeks produced clinically significant gastrointestinal (GI) steatorrhea, abdominal cramping and distention) and statistically significant hepatobiliary (elevated liver function tests and minor fatty liver) symptoms in some patients receiving study drug. It appeared that the degree of both GI-related symptoms and hepatic fat were in part due to the study design, particularly the dosing regimen. BMS-201038 is a potent inhibitor of both intestinal and hepatic microsomal triglyceride transfer protein (MTP). While lack of adequately controlling dietary fat intake most likely contributed to GI-related symptoms, it is possible that providing a starting dose of 25 mg/day also contributed. Starting at a low dose and titrating up slowly may improve GI-related tolerability as well as provide time for the liver to adjust to the inhibition of MTP, perhaps decreasing hepatic fat build up. This theory was applied in designing a study investigating the safety, tolerability and efficacy of BMS-201038 in patients with homozygous familial hypercholesterolemia (hoFH).

[0097] Six patients with hoFH were enrolled and completed the study per protocol. Subjects received once daily dosing of 4 doses of BMS-201038 (0.03, 0.1, 0.3 and 1.0 mg/kg) for 4 weeks at each dose. We chose an initial low dose (0.03 mg/kg) that while not expecting to be efficacious, would be a dose that would be expected to be safe and well tolerated (~2.1 mg in the 70 kg man). The remaining three doses were chosen by calculating ½ log units of the previous dose. We picked an upper dose of 1 mg/kg based on data from the animal study by Wetterau and colleagues revealing greater than 80% LDL cholesterol reduction using 10 mg/kg, with an ED_{50} of 1.9 mg/kg. All 6 subjects tolerated the drug up to the maximal 1 mg/kg dose with little to no steatorrhea. Although all subjects had evidence of dose-dependent increases in hepatic fat by NMRS, the increase from baseline to 4 weeks on 1 mg/kg was varied with a range of 3-37%. Three of 6 subjects experienced substantial increases in liver transaminases, but only 1 subject had a persistent increase that required a temporary dose reduction. This subject also had the greatest increase in hepatic fat which

may have been exacerbated by the large consumption of alcohol on a regular basis. At the two highest doses, the mean percent changes in lipids among the 6 subjects were: total cholesterol -30 ± 9% and -58 ± 8.5%, non-HDL cholesterol -31 ± 9% and -60 ± 8.8%, and apoB -15 ± 16% and -55 ± 13%, respectively. These data indicate that symptoms of steatorrhea and hepatic fat can be significantly reduced by initiating a low dose with a gradual up titration.

[0098] Each of the patents, patent applications, and publications described herein is hereby incorporated by reference in its entirety.

[0099] Various modifications of the invention, in addition to those described herein, will be apparent to those of skill in the art in view of the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:

1. A method of treating a subject suffering from a disorder associated with hyperlipidemia, said method comprising administering to the subject an effective amount of an MTP inhibitor to ameliorate hyperlipidemia in said subject, wherein said administration comprises at least three step-wise, increasing dosages of the MTP inhibitor.

2. The method of claim 1 in which the disorder associated with hyperlipidemia is hypercholesterolemia.

3. The method of claim 2 wherein hypercholesterolemia is homozygous/heterozygous familial hypercholesterolemia.

4. The method of claim 1, in which the disorder associated with hyperlipidemia is hypertriglyceridemia.

5. The method of claim 1 wherein cholesterol levels in said subject are reduced by at least 25%.

6. The method of claim 1 wherein triglyceride levels in said subject are reduced by at least 25%.

7. The method of claim 1wherein apolipoprotein B (apo B) levels in said subject are reduced by at least 25%.

8. The method of claim 1 wherein said subject is refractory to traditional treatments for hyperlipidemia.

9. The method of claim 5 wherein said triglyceride level achieved is less than 500 mg/dl.

10. The method of claim 5 wherein said triglyceride level achieved is less than 300 mg/dl.

11. The method of claim 5 wherein said triglyceride level achieved is less than 200 mg/dl.

12. The method of claim 5 wherein said triglyceride level achieved is less than 150 mg/dl.

13. The method of claim 1 wherein the MTP inhibitor lowers plasma LDL-cholesterol to at least 50% of normal LDL blood levels, and lowers triglycerides to at least 50% of normal triglyceride blood levels.

14. The method of claim 1 wherein said MTP inhibitor has a structure as set forth in U.S. Patent 6,066653.

15. The method of claim 1 wherein said MTP inhibitor is administered orally.

16. The method of claim 1 wherein said escalating doses comprise at least a first dose level, a second dose level, and a third dose level.

17. The method of claim 16 wherein said escalating doses further comprise a fourth dose level.

18. The method of claim 17 wherein said each dose level is no more than 50% of the immediately following dose level.

19. The method of claim 17 wherein said each dose level is no more than 33% of the immediately following dose level.

20. The method of claim 17 wherein said first dose level is from about 0.02 to about 0.059 mg/kg/day.

21. The method of claim 17 wherein said second dose level is from about 0.06 to about 0.19mg/kg/day.

22. The method of claim 17 wherein said third dose level is from about 0.2 to about 0.59 mg/kg/day.

23. The method of claim 18 wherein said fourth dose level is from about 0.6 to about 2.0 mg/kg/day.

24. The method of claim 16 wherein each dose level is administered to said subject for 1-5 weeks.

25. The method of claim 16 wherein each dose level is administered to said subject for 2 days to about 3 months.

26. The method of claim 1 wherein an ApoB/ApoA1 ratio achieved is from 0.25 to 1.25.

27. The method of claim 1 wherein an ApoB/ApoA1 ratio achieved is from 0.1 to 2.0.

28. The method of claim 1 wherein an apoB level achieved is from 48-130.

29. The method of claim 1 wherein an apoB level achieved is from 20-180.

30. The method of claim 1 wherein one or more of Total Cholesterol, high density lipoprotein (HDL) cholesterol, fasting triglycerides (TG), very low density lipoprotein (VLDL), lipoprotein (a) (Lp(a)), and apolipoproteins A-I, A-II, B, and E are reduced by at least 30%.

31. The method of claim 1 wherein said MTP inhibitor is administered at:

(a) 0.03mg/kg/day for a first interval;

(b) 0.1 mg/kg/day for a second interval;

(c) 0.3 mg/kg/day for a third interval; and

(d) 1.0 mg/kg/day for a fourth interval.

32. The method of claim 31 wherein the first, second, third, and fourth intervals are each from about 2 days to about 40 days in duration.

33. The method of claim 31 wherein the first, second, third, and fourth intervals are each from about 7 days to about 35 days in duration.

34. The method of claim 31 wherein the first, second, third, and fourth intervals are from about 2 weeks to about 4 weeks in duration.

35. The method of claim 31 wherein the first, second, third, and fourth intervals are each about 4 weeks in duration.

36. The method of claim 31 wherein the first, second, third intervals are from about 2 days to about 40 days in duration and the fourth interval is from about 2 days to about 6 months in duration.

37. The method of claim 17 wherein the first dose level is 6.25 mg/day, the second dose level is 12.5mg/day, and the third dose level is 50mg/day.

38. The method of claim 37 wherein each dose level is administered to the subject from about 1 week to about 12 weeks.

39. The method of claim 37 wherein each dose level is administered to the subject from about 1 week to about 26 weeks.

40. The method of claim 37 wherein the first does level is administered for 2 weeks, the second dose level administered for 4 weeks, and the third dose level administered for 4 weeks.

41. The method of claim 37 wherein the subject weighs less than 62.5kg.

42. The method of claim 37 further comprising a fourth dose level of 62.5mg/day for 4 to about 26 weeks.

43. The method of claim 37 further comprising a fourth dose level of 75 mg/day for 4 to about 26 weeks.

44. A method for inhibiting MTP in a subject comprising administering to the subject an effective amount of an MTP inhibitor to inhibit MTP in said subject, wherein said administration comprises at least three step-wise, increasing dosages of the MTP inhibitor.

45. The method of claim 44 wherein the MTP inhibitor is administered orally.

46. The method of claim 1 wherein said inhibitor is administered to said subject in combination with a traditional medicament for the treatment of hyperlipidemia.

47. A kit for treating a disorder related to hyperlipidemia in a subject, comprising:

a) a pharmaceutical composition comprising at least three sets of dosage units, wherein a first set of dosage units provides 0.03mg/kg/day for a first interval, a second set of dosage units provides 0.1 mg/kg/day for a second interval, and a third set of dosage units provides 0.3 mg/kg/day for a third interval;

b) instructions for use.

48. The kit of claim 47 further comprising a fourth set of dosage units, said fourth set providing 1.0 mg/kg/day for a fourth interval.

49. The kit of claim 47 further comprising a container for storing the sets of dosage units according to a schedule for administration.

50. The method of claim 1 or 46 wherein the inhibitor is BMS-201038.

51. The method of claim 1 wherein total cholesterol is reduced by at least 30%.

52. The method of claim 1 wherein non-HDL cholesterol is reduced by at least 30%

53. The method of claim 1 wherein apoB is reduced by at least 15%.

54. The method of claim 1 wherein LDL-Cholesterol is reduced by at least 30%.

55. The method of claim 16 wherein each dose level is administered to said subject for the same duration of time.

56. The method of claim 1 wherein said escalating doses comprise at least a first dose level and a second dose level.

57. The method of claim 56 wherein said each dose level is no more than 50% of the immediately following dose level.

58. The method of claim 56 wherein said each dose level is no more than 33% of the immediately following dose level.

59. The method of claim 56 wherein said first dose level is from about 0.02 to about 0.59 mg/kg/day.

60. The method of claim 56 wherein said second dose level is from about 0.06 to about 2.0 mg/kg/day.

61. The method of claim 56 wherein each dose level is administered to said subject for 1-5 weeks.

62. The method of claim 56 wherein each dose level is administered to said subject for 2 days to about 3 months.

63. The method of claim 56 wherein the first interval is from about 2 days to about 40 days in duration and the second interval is from about 2 days to about 6 months in duration.

ABSTRACT

[00100] The present invention provides methods and compositions for treating hyperlipidemia and/or hypercholesterolemia comprising administering to the subject an effective amount of an MTP inhibitor to inhibit hyperlipidemia and/or hypercholesterolemia in said subject, wherein said administration comprises an escalating series of doses of the MTP inhibitor. In some embodiments the method comprises administering at least three step-wise, increasing dosages to the subject. In some embodiments the inhibitor is BMS-201038.